Heriot-Watt University
Research Gateway

Effects of solvents and impurity on crystallization kinetics and crystal properties in a reactive crystallization of paracetamol

Citation for published version:
Jiang, M & Ni, X-W 2019, 'Effects of solvents and impurity on crystallization kinetics and crystal properties in a reactive crystallization of paracetamol', *Journal of Crystal Growth*, vol. 523, 125150.
https://doi.org/10.1016/j.jcrysgro.2019.125150

Digital Object Identifier (DOI):
10.1016/j.jcrysgro.2019.125150

Link:
Link to publication record in Heriot-Watt Research Portal

Document Version:
Peer reviewed version

Published In:
Journal of Crystal Growth

Publisher Rights Statement:
© 2019 Elsevier B.V.

General rights
Copyright for the publications made accessible via Heriot-Watt Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
Heriot-Watt University has made every reasonable effort to ensure that the content in Heriot-Watt Research Portal complies with UK legislation. If you believe that the public display of this file breaches copyright please contact open.access@hw.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 05. May. 2023

Accepted Manuscript

Effects of solvents and impurity on crystallization kinetics and crystal properties in a reactive crystallization of paracetamol

Meifen Jiang, Xiong-Wei Ni

PII: S0022-0248(19)30357-4
DOI: https://doi.org/10.1016/j.jcrysgro.2019.125150
Article Number: 125150
Reference: CRYS 125150

To appear in: *Journal of Crystal Growth*

Received Date: 7 March 2019
Revised Date: 28 June 2019
Accepted Date: 2 July 2019

Please cite this article as: M. Jiang, X-W. Ni, Effects of solvents and impurity on crystallization kinetics and crystal properties in a reactive crystallization of paracetamol, *Journal of Crystal Growth* (2019), doi: https://doi.org/10.1016/j.jcrysgro.2019.125150

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Effects of solvents and impurity on crystallization kinetics and crystal properties in a reactive crystallization of paracetamol

Meifen Jiang and Xiong-Wei Ni*

EPSRC Centre for Continuous Manufacturing and Crystallization (CMAC), Centre for Oscillatory Baffled Applications (COBRA), School of Engineering and Physical Sciences, Heriot-Watt University, Edinburgh, EH14 4AS, U.K.

* the corresponding author, tel: 00441314513781, email: x.ni@hw.ac.uk

Abstract: The effect of three solvents which are mixtures of water and acetic acid of different compositions on crystallization kinetics and crystal properties is reported. The nucleation orders for the three solvents used in this work are comparable, but higher than published data. The growth rates are similar to that of recrystallization work. Different solvents can deliver the same supersaturation, but crystal shapes change from column to needle-like. Different solvent compositions can also give rise of different levels of impurity due to the side reaction, their effects on crystal morphology and purity are discussed. We demonstrate that the reagents and solvents from the reaction step are the means for controlling and delivering required crystal properties when both reaction and crystallization are carried out in a continuous fashion.

Keywords: A1. Solvents; A1. Impurities; A1. Crystal morphology; A1. Nucleation; A2. Growth form solutions; A2. Industrial crystallization

1. Introduction

Paracetamol (acetaminophen) is a widely used analgesic drug in the world today and is usually manufactured by a reactive crystallization process. The reaction part involves

ACCEPTED MANUSCRIPT

acetylating 4-aminophenol with a small stoichiometric excess of acetic anhydride in an aqueous medium[1, 2]; the separation and purification of paracetamol is achieved via recrystallization using cooling and anti-solvent means[3-5]. The focus of this work is on continuous reactive crystallization where two separate unit operations are combined and done in a nonstop manner. In this respect, reaction conditions have a significant effect on crystallization kinetics that have rarely been examined. Our previous study presented the effect of water content and reaction temperature on crystallization properties, however, crystallization kinetics have not been fully investigated under different reaction conditions[6]. In this work, the ratios of reactants are determined based on the solvent compositions that deliver the optimized solubility for crystallization. By comparing nucleation and growth kinetics for different solvents that are directly generated from the reaction, the effects of paracetamol synthesis on crystallization kinetics and crystal morphologies are jointly investigated, i.e. we link the reaction with crystallization as a single process, these are new to previous separated studies of either reaction or recrystallization.

2. Basic concepts of nucleation and growth kinetics

2.1. Nucleation kinetics

Nucleation kinetics are commonly estimated using the classical Nývlt equation[7-9] where the nucleation rate (J) is related to the maximum solution supersaturation (Δc_{max}), in turn, the maximum supercooling (ΔT_{max}), with cooling rate (r) (°C h^{-1}). However, the limitation for the Nývlt approach is that the derivation is based on the assumption that the solubility coefficient (dc/dT) is independent of the saturation temperature (T_0) (°C), leading to concentration-based units for the nucleation rate, in turn complicated units with non-physical significance for the nucleation order and constant. Consequently, a self-constant Nývlt equation[10, 11] was proposed, which utilizes a dimensionless maximum supercooling ($\Delta T_{max}/T_0$) as:

$$ln\left(\frac{\Delta T_{max}}{T_0}\right) = \frac{1}{b}ln\, r + \frac{1-b}{b}ln\left(\frac{\Delta H}{RT_n}\right) + \frac{1}{b}\left(ln\frac{f}{k}\right) - \frac{1}{b}lnT_0 \quad (1)$$

where ΔH is the heat of dissolution (KJ mol^{-1}), R the gas constant (J mol^{-1}K^{-1}), T_n the nucleation temperature (K) and f the proportionality constant. A linear relationship between

ACCEPTED MANUSCRIPT

ln ($\Delta T_{max}/T_0$) and ln r enables the determination of nucleation order from the slope $1/b$. The main advantage of Eq. (1) is that the effect of saturation temperature T_0 on (dc/dT) is included.

2.2. Growth kinetics

Crystal growth kinetics are important in the design and development of crystallization processes and many different theories have been employed to facilitate crystal growth mechanisms[7].While there is no general accepted method for expressing the growth kinetics, crystal growth rate, G (m s^{-1}), in terms of mass deposited per unit time per unit area of crystal surface is used in this work as[7]:

$$G = K_G \frac{\beta}{3\alpha\rho_c} (\ln S)^g \quad (2)$$

where K_G, ρ_c and g are the overall mass transfer coefficient (kg m^{-2} s^{-1}), crystal density (kg m^{-3}) and growth order, respectively. The growth rate is related to the level of supersaturation in terms of a dimensionless concentration of , where $S = c/c^*$, c is the concentration in solution (kg $_{solute}$ kg^{-1} $_{solvent}$) and c^* refers to solubility at the same temperature (kg $_{solute}$ kg^{-1} $_{solvent}$).

3. Experimental section

3.1. Materials

4-Aminophenmol (4-AP) (Sigma Aldrich UK Ltd.; purity, ≥ 99 %; MW, 109.13 g mol^{-1}) was sourced in the form of light brown crystalline solid. Paracetamol (PARA) (GlaxoSmithKline Pharmaceutical Company; purity, 99.8 %; MW, 151.16 g mol^{-1}) was purchased for the purpose of calibration of HPLC device, and 4'-Acetoxyacetanilide (PAA) (TCI AMERICA; purity, ≥99.0 %; MW, 193.20 g mol^{-1}) for the identification and calibration of the intermediate product. Acetic anhydride (AA) (purity, 99+ % pure; MW, 102.09 g mol^{-1}), methanol (purity, HPLC grade; MW, 32.04 g mol^{-1}) and distilled water (resistivity, 18.2 MΩ cm at 25ºC; density, 1 g cm^{-3}; MW, 18.02 g mol^{-1}) were also applied.

ACCEPTED MANUSCRIPT

3.2. Characterization

The concentration of paracetamol was analyzed by the Agilent1100 Series HPLC System, and the chromatograph column was a reverse phase ZORBAX SB-C8 (4.6×150 mm; 5 µm packing). The UV detector was set at 243 nm and the mobile phase running throughout the system was a mixture of methanol and water with a mass ratio of 1:3. HPLC measurements were operated at room temperature, sample injection volume was 1 µL. Fig. 1 below shows that the peak of paracetamol appears after 5 minutes at a flowrate of 0.8 ml min^{-1}. Subsequently a calibration curve was developed and a good linear relationship between the peak areas and concentration of paracetamol is seen, i.e. Concentration = (Peak Area – 3.8927) ÷24833.

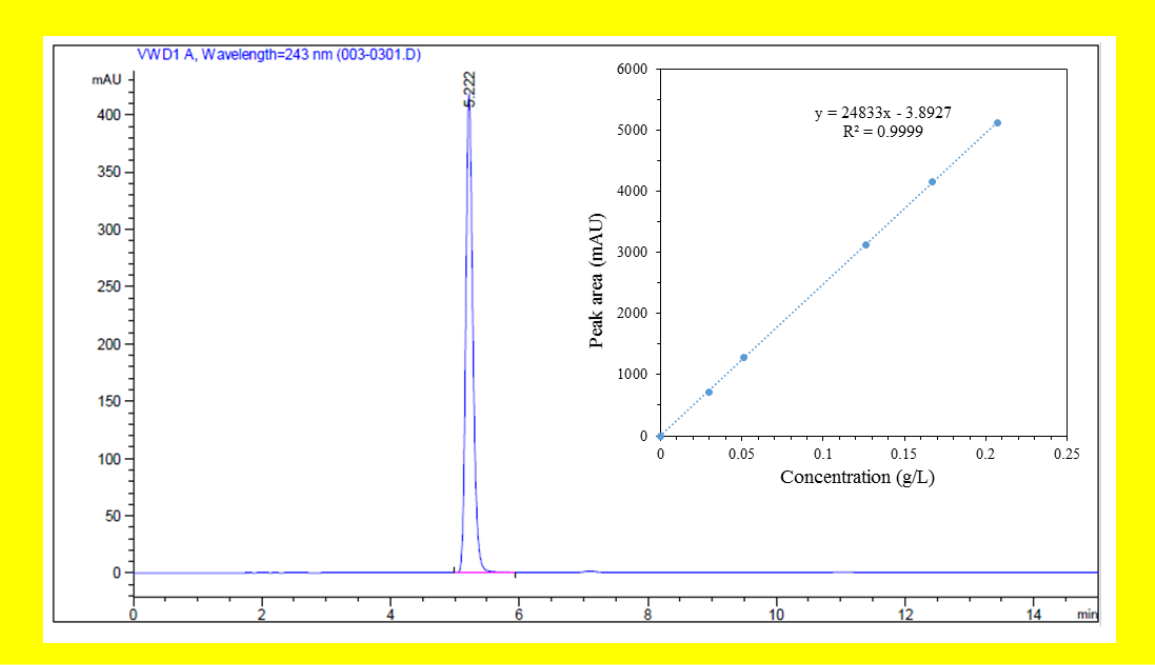

Fig.1. HPLC measurement for paracetamol standard solution with a calibration curve

The crystal size distributions were obtained by a Mastersizer 3000™ (HYDRO, Malvern). The dispersion fluid for Mastersizer operation is hexane and isopropanol is used for washing. The agitation rate is 2000 rpm without ultrasound. Morphologies of crystals by a

ACCEPTED MANUSCRIPT

Leica ATC 2000 Trinocular Microscope, crystal surface properties by scanning electron microscope (SEM) and crystal polymorphs by Power X-Ray Diffraction (PXRD).

3.3. Equipment for reactive crystallization

Reactive crystallization of paracetamol was performed in a jacketed oscillatory baffled reactor (OBR) (Fig. 2) with an internal diameter of 76 mm and a working volume of 1 L. A baffle string consists of 2 orifice baffles with orifice diameter and baffle space of 32 mm and 86 mm respectively, giving a baffle free area ratio of 0.21. A linear actuator connecting to the baffle string delivers different oscillation amplitudes and frequencies. The temperature within the OBR was controlled by a water bath (Grant Instruments GP 200/R2), enabling different linear cooling rates. The metastable zone width was determined from turbidity measurements using an online turbidity probe (METTLER TOLEDO). The schematic illustration of the OBR is shown in Fig. 2.

The procedures involve charging different amounts of 4-aminophenol, acetic anhydride and water into the preheated OBR at 50 °C under oscillation. The reactions were commenced when the OBR was further heated up and maintained at 75 °C. Samples were taken at regular time intervals using a pipette with an accurate volume of 0.30 ml; and were quenched and diluted 100 times with the mobile phase solution (methanol : water = 1:3). The overall reaction time was about 40 minutes; after which the crystallization was immediately initiated by cooling the solution to 20 °C at different cooling rates.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

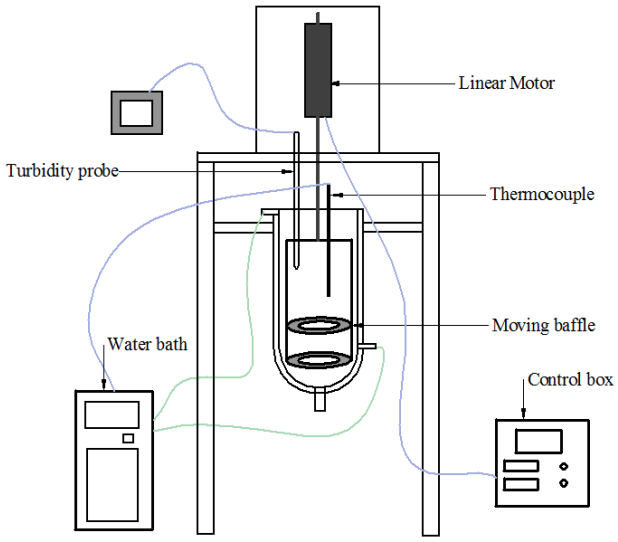

Fig. 2. Schematic of OBR setup

4. Results and discussions

4.1. Solvent composition and paracetamol solubility

Paracetamol is produced by reacting 4-aminophenol and acetic anhydride with acetic acid as a side product when water reacts with the excessive acetic anhydride. The reaction scheme was discussed previously[6] and shown in Fig. 3. Paracetamol solubility in the mixture of acetic acid and water at different ratios are illustrated in Fig.4. It is as expected that the solubility of paracetamol increases with temperature. Meanwhile, as the ratio of acetic acid to water increases, the capacity of paracetamol in the mixed solvent increases and reach to a maximum value at Acid:H_2O = 7:3, and then declines with increasing acid content. This is due to the dissociation ability of acetic acid in the aqueous solution. Since acetic acid is a weak acid, only a small fraction of the acetic acid molecules can react with water to form ethanoate and hydronium ions. This equilibrium position lies well to the left before paracetamol is dissolved in the mixed solvent. The interactions among paracetamol, acetic acid and water molecules induces the reaction to the right direction, leading to the rising

ACCEPTED MANUSCRIPT

solubility of paracetamol at low acetic acid content, and low solubility when there is insufficient water.

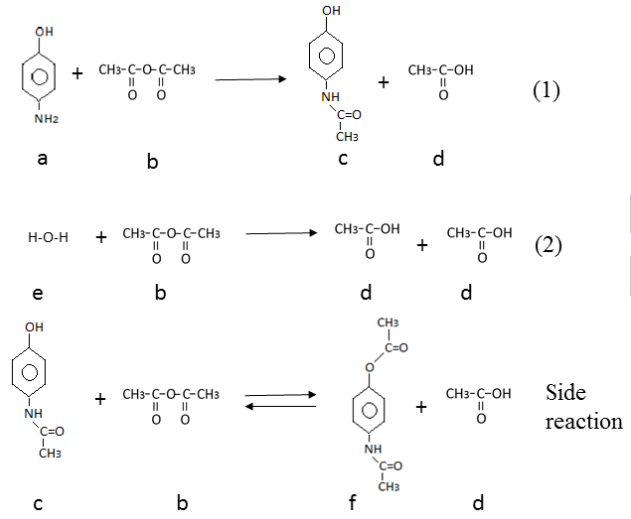

Fig. 3. Reaction scheme for paracetamol synthesis[6]. a: 4-aminophenol (4-AP); b: acetic anhydride (AA); c: paracetamol; d: acetic acid; e: water; f: 4'-acetoxyacetanilide (PAA).

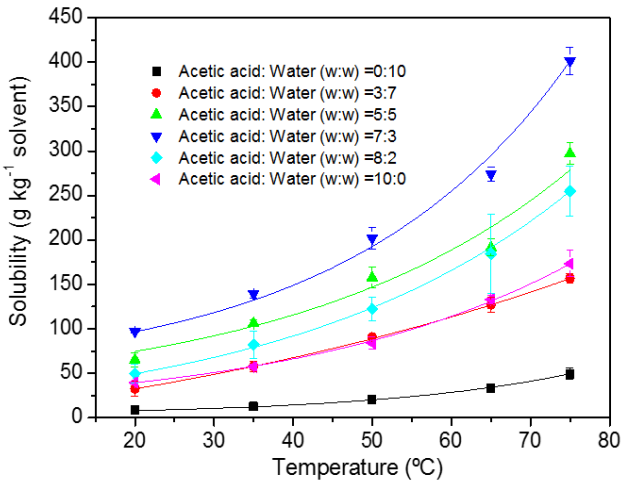

Fig. 4. Solubility of paracetamol in different ratios of acetic acid to water

ACCEPTED MANUSCRIPT

Fig.5A is the HPLC chromatogram for one of the samples where three peaks at retention time of 3.695, 5.193 and 11.286 min correspond to the solvent, paracetamol, and 4'-acetoxyacetanilide (PAA) respectively, from which concentrations of paracetamol and 4'-acetoxyacetanilide changing with time are obtained as shown in Fig. 5B. We see that the concentration of paracetamol increases dramatically in the first 10 minutes and then stabilizes at an average value of 65.23 g L^{-1} before it falls, this is the initial concentration for crystallization. The solute concentration continues decreasing thereafter as more paracetamol particles are formed during crystallization. We also see that the generation of the by-product (PAA) via the side reaction (Fig.3) is continuous from the start, but at a much lower concentration than that of the target compound (Fig.5B). PAA acts as an impurity for crystallization step, as the concentration of which in solution stays constant while the concentration of paracetamol is decreasing. No visible impurity was observed on product crystals in both HPLC and NMR analysis, and a purity of 99 % was achieved.

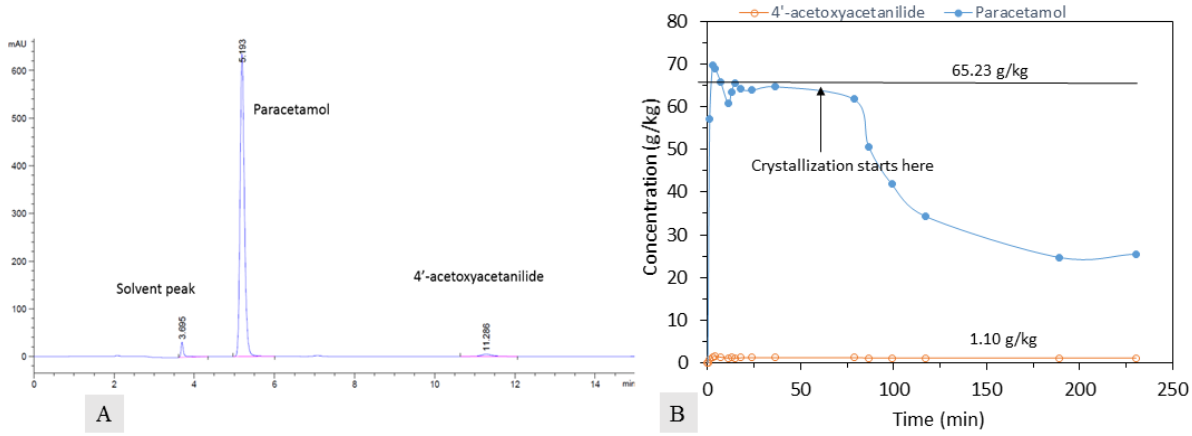

Fig.5. (A) HPLC chromatogram showing solvent, paracetamol and 4'-acetoxyacetanilide (PAA) peaks; (B) Concentrations of paracetamol and impurity (PAA) as a function of time

From the reaction scheme in Fig. 3, the solvent for crystallization is a mixture of acetic acid and water that are directly generated from the reaction step, different ratios of which give different solubility as shown in Fig. 4 with the highest at 7:3 (acetic acid : water). In this work, the effects of three acid to water ratios (1:9, 5:5 and 7:3) on crystallization kinetics and crystal properties were examined. The amounts of reactants, i.e. the ratio of 4-aminophenol

ACCEPTED MANUSCRIPT

(4-AP) to acetic anhydride (AA), required to produce paracetamol in any of the above solvent ratios were back calculated according to the reaction stoichiometry and solubility profile (see the row two in Table 1). This is how the reaction is linked with crystallization. Table 1 shows the various parameter settings for both reaction and crystallization conditions. Note that various reactant ratios of 4-AP: AA can generate the same solvent ratio, e.g. the same ratio of acetic acid: water of 1.9 can be obtained via four ratios of 4-AP: AA (see the rows 1-2 in column 2 of Table 1), this adds the complexity of our study, also increases the number of experiments carried out.

Table 1. Experimental conditions used for reactive crystallization of paracetamol

Acid : H_2O (w : w)	1:9				5:5			7:3		
AA : 4-AP (mol : mol)	1.8	2	2.3	2.7	1.8	2	2.3	1.8	2.3	2.7
Cooling rate (°C min^{-1})	0.8	0.8	0.4, 0.8, 1.2	0.8	0.8	0.4, 0.8, 1.2	0.8	0.4, 0.8, 1.2	0.8	0.8
Frequency (Hz)	1	1	0.5, 1.0, 2.0	1	1	0.5, 1.0, 2.0	1	0.5, 1.0, 2.0	1	1
Amplitude (mm)	44	44	44	44	44	44	44	44	44	44

4.2. Effect of solvent on nucleation kinetics

Fig. 6 plots ln ($\Delta T_{max}/T_0$) vs ln r from Eq. (1) for three solvent ratios of 1:9, 5:5 and 7:3, respectively. We see that the metastable zone width (ΔT_{max}) increases for every solvent system as the cooling rate (r) increases from 0.4 to 1.2 °C h^{-1}. At a given cooling rate, the lower the ratio of Acid: H_2O, the wider the MSZW, indicating that the MSZW can be controlled by the solvent compositions from the reaction step. The influences of solvents on nucleation kinetics were investigated in recrystallization work: the net effect of changing solvent led to an increase of solubility, in turn an increase of nucleation rate due to the

ACCEPTED MANUSCRIPT

decrease of interfacial tension between solute and solvent on specific faces[12]. Nucleation order (b) is highly dependent on the solubility of a solute in a given solvent[11]; and is 5.4, 15.5 and 14.1 in this work for the three solvents respectively, which are higher than 1.68 for paracetamol in ethanol by Mitchell and Frawley[13]; and 0.6 – 3.4 for paracetamol in methanol/water solutions by Ó'Ciardhá et al.[14] Higher nucleation orders in this research are related to higher solubility of the solvents used, which leads to different levels of supersaturation. Moreover, agglomeration also contributes to high nucleation orders, the effect of which is still difficult to be separated using current PAT tools.

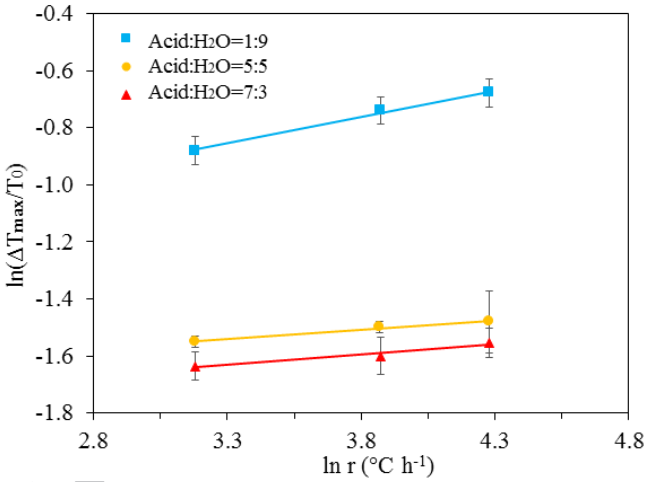

Fig. 6. Plot of ln ($\Delta T_{max}/T_0$) vs ln r for three solvents

4.3. Effect of solvent on growth kinetics

In this work, the overall growth rate was determined by plotting crystals size as a function of time. Mastersizer was used for crystal size measurements for samples that took at regular time intervals once nucleation was observed in the solution. By plotting the overall linear growth rate (G) against the supersaturation (c/c^*) from Eq. (2), Fig. 7 shows the increase of the growth rate with the supersaturation for each solvent composition. Our data are in the similar order of magnitude, but higher than others of recrystallization of paracetamol in various solutions[15-18]. Reactive crystallization of paracetamol in a stirred tank with

ACCEPTED MANUSCRIPT

sodium hydroxide added after the reaction step gave the growth rates from 4.04 to 5.64 × 10^{-8} m s^{-1} using a sieving method[19], which are similar to our data (see Fig. 7).

The growth orders (g) were extracted from the power law relationship displayed in Fig. 7 as 4.27, 12.62, and 1.72 respectively for the three solvents. We see that there is no direct dependence of crystal growth order on the solvent composition. Ó'Ciardhá et al. [16] reported that solvent composition, solubility gradient and viscosity all contributed to crystal growth machanisms, where solvent may decrease growth rate due to the selective absorption of solvent molecules, or enhance face growth rate by causing a reduction in the interfacial tension, leading to an unclear role played by solvent in affecting crystal growth[16, 20].

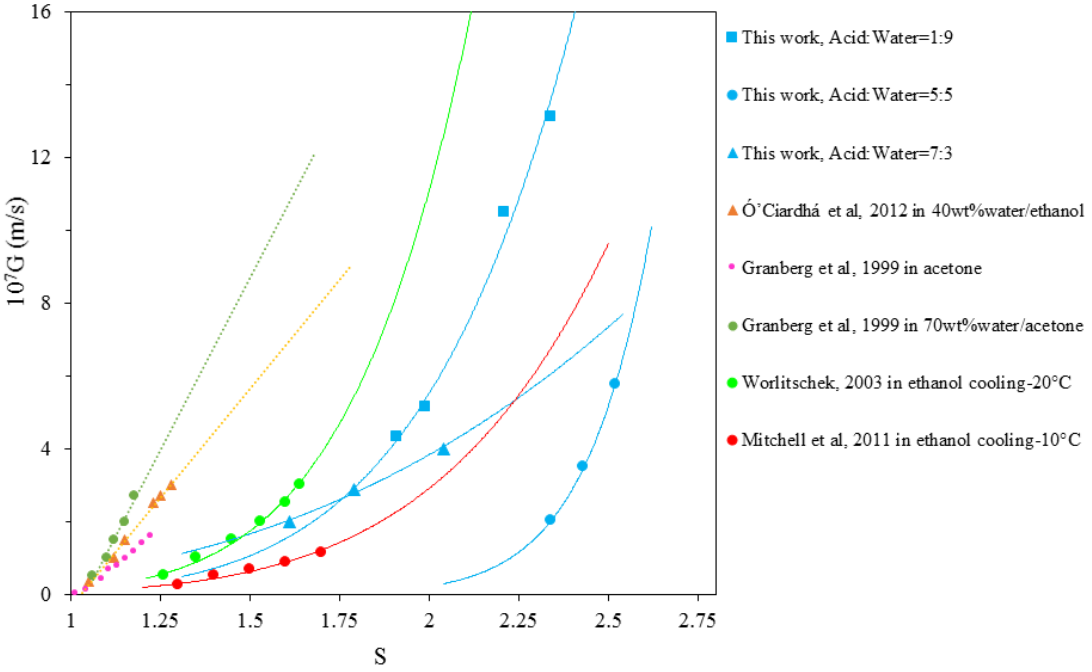

Fig. 7. Comparison of growth rates between this work and previous researches

The main differences of this work with respect to past papers are that solvent compositions for crystallization in our work are directly produced from the reaction step, by varying the ratios of reactants (AA : 4-AP) at the start of the reaction, the control of supersaturation is achieved, connecting the reaction with the crystallization as a single process.

ACCEPTED MANUSCRIPT

4.4. Effect of solvent on crystal shape

The effect of solvent ratios generated from the reaction on crystal shape is shown in Fig. 8. Rectangle column type of crystals is seen at the low ratio of Acid: H_2O. The columns become longer and thinner as the ratio increases. The crystal shape classification diagram by Li and Doberty [21] according to different functional groups of solvents also predicted the elongated shape for solvents of class 1 (involving acetic acid) and class 6 (water) with aspect ratios of crystals >3. However, higher aspect ratios of crystals in our work were generated in solvents of higher dispersive energies, e.g. water, this is different from the reported predictions and could be due to the increased concentrations of both paracetamol and impurity (PAA).

From the SEM graphs (Fig. 8), the lengths and diameters of over 30 crystals were measured microscopically, leading to the determination of the specific surface factors for crystals as 6.37, 5.31 and 4.75 for the three solvent systems respectively, which are comparable to 6.27~7.70 for rounded hexagonal crystals by Granberg and Rasmuson[22].

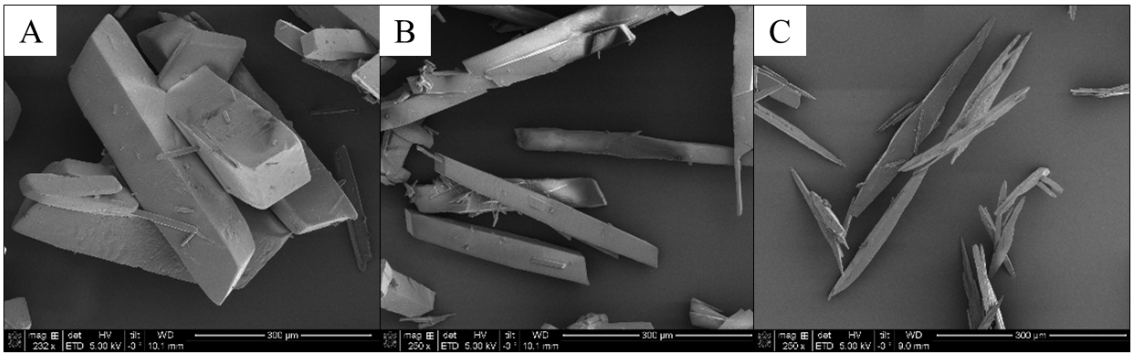

Fig.8. SEM measurements for paracetamol crystals in three solvents: (A) Acid: H_2O = 1:9, S = 1.99; (B) Acid: H_2O = 5:5, S = 2.34; (C) Acid: H_2O = 7:3, S = 2.04

4.5. Effect of impurity on crystal shape

In the reactive crystallization, the solubility for crystallization (Fig.4) results from different solvent compositions that are formed by the reaction; the concentrations of paracetamol (the product) and 4'-acetoxyacetanilide (PAA – the side product) are also

ACCEPTED MANUSCRIPT

generated as given in Table 2. At a constant solvent composition, the increase of the reagent ratio of AA:4-AP decreases the concentrations of paracetamol and PAA, leading to different supersaturation for crystallization, in turn different crystal morphologies as seen in Fig. 9, where smaller and finer crystals are expected when supersaturation increases. In this respect, the amount of impurity (PAA) is related to the supersaturation of paracetamol. At the same solvent ratio, product crystals change from plate-like to elongated, indicating the influence of PAA on crystal growth, this agrees with previous research[23].

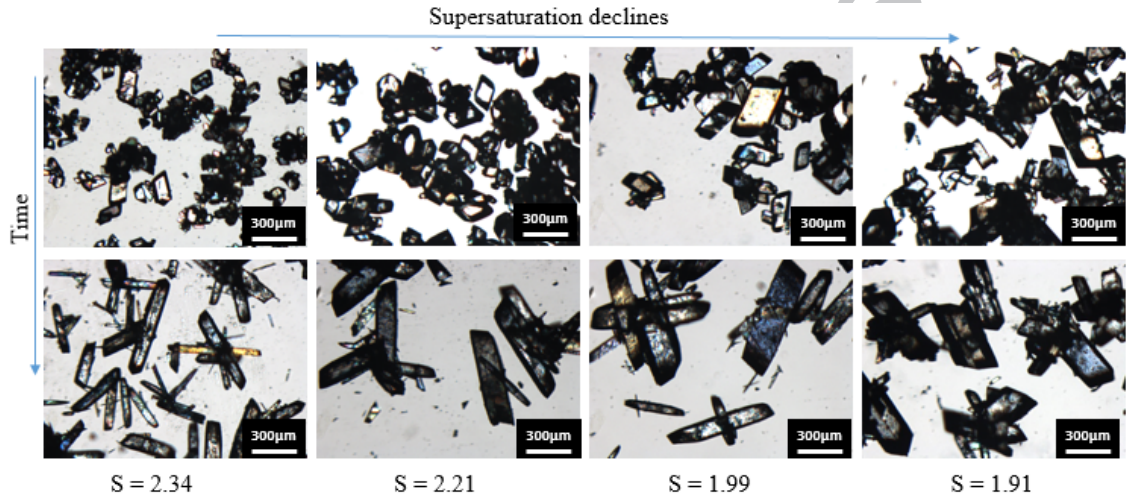

Fig. 9. Microscope images showing the effect of PAA on paracetamol crystal shapes for different supersaturation conditions at a fixed solvent ratio of Acid: H_2O = 1:9

Table 2. PARA and PAA concentrations in different solvent compositions by reaction

Acid : H_2O (w : w)	1:9				5:5			7:3		
AA : 4-AP (mol : mol)	1.8	2	2.3	2.7	1.8	2	2.3	1.8	2.3	2.7
PARA (mol kg^{-1})	0.599	0.514	0.441	0.375	2.029	1.96	1.803	2.382	2.214	2.004
PAA (mol kg^{-1})	0.006	0.006	0.005	0.005	0.158	0.093	0.052	0.233	0.137	0.105

ACCEPTED MANUSCRIPT

Some agglomerations are observed (Fig. 8), with a lesser degree for solvents of higher Acid: H_2O ratios. Different solvent systems have different polarities due to the interactions with H-bonding at crystal surfaces, e.g. polar solvents have stronger interactions, reducing the formation of crystalline bridges. For this work, the Acid: H_2O ratio of 1:9 has the highest polarity, but the degree of agglomeration is also high. This is opposite to previous work where agglomeration was found weaker for more polar solvents[24]. This could attribute to the fact that the adhesion of the side product PAA in solution prevented the association of solvent molecules from depositing on crystal surfaces. Depending on the ratios of the starting materials, the concentrations of PAA increase with the increase of the ratios of Acid: H_2O as shown in Table 2.

4.6. Purity of crystal products

The purity of crystal products is plotted as a function of the reagent ratio in Fig.10. We see that the purities are generally high for all three solvents, with the highest purity of 99.84% at the Acid: H_2O ratio of 1:9 for all reactant ratios of AA: 4-AP. For the Acid: H_2O ratios of 5:5 and 7:3, product purity increases with the ratio of the starting materials. At the same reactant ratio of AA: 4-AP, crystal purity decreases with the increase of the Acid: H_2O ratios from 1:9 to 7:3. This indicates that solvents and PAA molecules are more likely to be absorbed onto crystal lattices at higher solubilities. Fig. 10 is a useful graph linking crystal purity (one of the crystal specifications) with the solvents for the crystallization and the starting materials for the reaction step. It is worth keeping in mind that all the product crystals in this work are monoclinic, which is polymorph Form I of paracetamol. This is confirmed by X-ray powder analysis and constant with previous published study on the reactive crystallization of paracetamol[6, 25].

ACCEPTED MANUSCRIPT

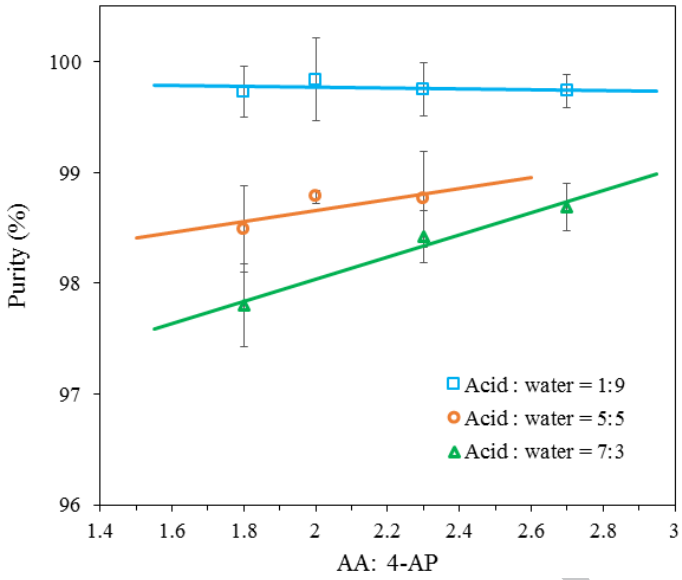

Fig. 10. Crystal purity as a function of AA: 4-AP ratios for different solvents

5. Conclusions

When solvent compositions for crystallization are directly produced from the reaction, we are able to examine the dependency of nucleation orders and growth rates on solvent compositions; a higher ratio of Acid:H_2O at the end of reaction leads to a higher nucleation order; growth rates are comparable with previous recrystallization data. Both solvent compositions and reagent ratios are the means for influencing crystal morphology: crystals shapes change from column to needle-like with the increase of solvent compositions. At a fixed solvent, three reagent ratios of AA:4-AP at the start of reaction deliver three supersaturations for crystallization with different levels of impurity, which affects crystal morphology and causes agglomerations.

Acknowledgement

ACCEPTED MANUSCRIPT

We acknowledge the financial support provided by the EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallization under Grant EP/K503289/1 and Heriot-Watt University.

Nomenclature

Δc_{max} = Maximum solution supersaturation (kg $_{solute}$ kg$^{-1}_{solvent}$)

b = Nucleation order

C = Mole fraction solubility of solute

c = Concentration in solution (kg $_{solute}$ kg$^{-1}_{solvent}$)

$c*$ = Solubility data at the same temperature (kg $_{solute}$ kg$^{-1}_{solvent}$)

dc/dT = Solubility coefficient

ΔH = Heat of dissolution (kJ mol^{-1})

f = Proportionality constant

G = Overall linear growth rate (m s^{-1})

g = Growth order

J = Nucleation rate (kg m^{-3} s^{-1})

k = Nucleation constant

k'= Growth rate constant

K_G = Overall mass transfer coefficient (kg m^{-2} s^{-1})

r = Cooling rate (°C h^{-1})

R = Gas constant (J mol^{-1} K^{-1})

S = Supersaturation ratio

T = Absolute temperature (K)

T_0 = Saturation temperature (°C)

T_n = Nucleation temperature (°C)

ΔT_{max} = Maximum supercooling (°C)

Greek letters

α = Crystal volume shape factor

β = Crystal surface shape factor

ACCEPTED MANUSCRIPT

ρ_c = Crystal density (kg m^{-3})

Compounds

4-AP = 4-Aminophenol
AA = Acetic anhydride
PAA = 4'-Acetoxyacetanilide
PARA = Paracetamol

References

[1] D.W. Young, Preparation of nu-acetyl-p-aminophenol, U.S. Patent 3113150, 1963.

[2] M. Srabovic, M. Huremovic, B. Catovic, S. Muratovic, A. Taletovic, Design synthesis and crystallization of acetaminophen, JCBPSC, 7 (1) (2017) 218-230.

[3] C.J. Brown, X. Ni, Online evaluation of paracetamol antisolvent crystallization growth rate with video imaging in an oscillatory baffled crystallizer, Cryst. Growth Des., 11 (3) (2011) 719-725.

[4] C.J. Brown, X. Ni, Determination of metastable zone width, mean particle size and detectable number density using video imaging in an oscillatory baffled crystallizer, CrystEngComm, 14 (8) (2012) 2944-2949.

[5] S. Ferguson, F. Ortner, J. Quon, L. Peeva, A. Livingston, B.L. Trout, A.S. Myerson, Use of continuous MSMPR crystallization with integrated nanofiltration membrane recycle for enhanced yield and purity in API crystallization, Cryst. Growth Des., 14 (2) (2013) 617-627.

[6] M. Jiang, X. Ni, Effects of water and temperature on reaction mechanism and crystal properties in a reactive crystallization of paracetamol, Chem. Eng. Process., 131 (2018) 20-26.

[7] J.W. Mullin, Crystallization, Butterworth-Heinemann: Oxford, 2001.

[8] K. Sangwal, Nucleation and Crystal Growth: Metastability of Solutions and Melts, John Wiley & Sons, Inc: Hoboken, 2018.

[9] J. Nývlt, Kinetics of nucleation in solutions, J. Cryst. Growth, 3 (1968) 377-383.

ACCEPTED MANUSCRIPT

[10] K. Sangwal, Recent developments in understanding of the metastable zone width of different solute− solvent systems, J. Cryst. Growth, 318 (1) (2011) 103-109.

[11] K. Sangwal, A novel self-consistent Nývlt-like equation for metastable zone width determined by the polythermal method, Cryst. Res. Technol., 44 (3) (2009) 231-247.

[12] R.A. Granberg, C. Ducreux, S. Gracin, Å.C. Rasmuson, Primary nucleation of paracetamol in acetone–water mixtures, Chem. Eng. Sci., 56 (7) (2001) 2305-2313.

[13] N.A. Mitchell, P.J. Frawley, Nucleation kinetics of paracetamol–ethanol solutions from metastable zone widths, J. Cryst. Growth, 312 (19) (2010) 2740-2746.

[14] C.T. Ó'Ciardhá, P.J. Frawley, N.A. Mitchell, Estimation of the nucleation kinetics for the anti-solvent crystallisation of paracetamol in methanol/water solutions, J. Cryst. Growth, 328 (1) (2011) 50-57.

[15] N.A. Mitchell, C.T. Ó'Ciardhá, P.J. Frawley, Estimation of the growth kinetics for the cooling crystallisation of paracetamol and ethanol solutions, J. Cryst. Growth, 328 (1) (2011) 39-49.

[16] C. Ó'Ciardhá, N. Mitchell, K. Hutton, P. Frawley, Determination of the crystal growth rate of paracetamol as a function of solvent composition, Ind. Eng. Chem. Res., 51 (12) (2012) 4731-4740.

[17] J. Worlitschek, M. Mazzotti, Model-based optimization of particle size distribution in batch-cooling crystallization of paracetamol, Cryst. Growth Des, 4 (5) (2004) 891-903.

[18] R.A. Granberg, D.G. Bloch, Å.C. Rasmuson, Crystallization of paracetamol in acetone–water mixtures, J. Cryst. Growth, 198 (1999) 1287-1293.

[19] T. Lee, H.Y. Lin, H.L. Lee, Engineering reaction and crystallization and the impact on filtration, drying, and dissolution behaviors: the study of acetaminophen (paracetamol) by in-process controls, Organic Process Research & Development, 17 (2013) 1168-1178.

[20] R. Ristic, S. Finnie, D. Sheen, J. Sherwood, Macro-and micromorphology of monoclinic paracetamol grown from pure aqueous solution, The Journal of Physical Chemistry B, 105 (2001) 9057-9066.

[21] J. Li, M.F. Doherty, Steady state morphologies of paracetamol crystal from different solvents, Crystal Growth & Design, 17 (2017) 659-670.

ACCEPTED MANUSCRIPT

[22] R.A. Granberg, Å.C. Rasmuson, Crystal growth rates of paracetamol in mixtures of water+ acetone+ toluene, AIChE journal, 51 (2005) 2441-2456.

[23] K.V. Prasad, R.I. Ristic, D.B. Sheen, J.N. Sherwood, Crystallization of paracetamol from solution in the presence and absence of impurity, International journal of pharmaceutics, 215 (2001) 29-44.

[24] E.M. Ålander, Å.C. Rasmuson, Mechanisms of crystal agglomeration of paracetamol in acetone− water mixtures, Ind. Eng. Chem. Res., 44 (2005) 5788-5794.

[25] M. Jiang, X. Ni, Reactive Crystallization of Paracetamol in a Continuous Oscillatory Baffled Reactor, Organic Process Research & Development, 23 (5) (2019) 882-890.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Highlights

- Solvents from reaction step affect crystallization kinetics and crystal properties
- Supersaturation for crystallization depends on ratios of reaction reagents
- Agglomeration is seen in solvents of lower ratios of acid to water
- Effects of side reaction on particles morphology and purity are discussed

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Notes

The authors declare no competing financial interest.

ACCEPTED MANUSCRIPT